



Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus; the estimated worldwide prevalence of HCV infection is 2% to 3%, which translates to an estimated 170 million infected individuals of whom approximately 3.2 million live in the United States.¹ Seven distinct HCV genotypes have been described.² Genotype 1 infection accounts for approximately 75% of infections in the United States and approximately 90% of infections among blacks.^{3,4} Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, through sexual intercourse, and from a mother to her infant; however, the relative efficiency of transmission by these routes varies substantially. Approximately, 20% to 30% of HIV-infected patients in the United States are coinfecting with HCV.^{5,6}

HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.⁷⁻⁹ Transmission via injection drug use remains the most common mode of acquisition in the United States while transmission through contaminated blood products is now rare. Health care-associated transmission of HCV also can occur as a result of improper reuse of parenteral medications and equipment.¹⁰⁻¹² Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Heterosexual transmission of HCV is uncommon but more likely in those whose partners are coinfecting with HIV and HCV.^{13,14} Existing data also suggest that sexual contact is a relatively inefficient mode of transmission between HIV seronegative men who have sex with men (MSM).¹⁵ However, in HIV-infected MSM, multiple outbreaks of acute HCV infection demonstrate that sexual transmission is an important mode of acquisition in this population.¹⁶ Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted diseases (STDs).^{15,17-19,20,21} Temporally, the increase in the incidence of sexual transmission of HCV among HIV-infected MSMs coincides with an increase in high-risk sexual behaviors following the introduction of antiretroviral therapy (ART).^{22,23}

Mother-to-child transmission of HCV infection occurs in approximately 1% to 3% of infants born to HCV-seropositive mothers without and 4% to 7% of infants born to HCV-seropositive mothers with detectable plasma HCV RNA levels.²⁴⁻²⁷ Incidence of mother-to-child HCV transmission is increased when mothers are HIV-coinfecting, reaching rates of 10% to 20%.^{28,29}

Clinical Manifestations

Both acute and chronic HCV infections are usually minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have characteristic symptoms, including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels may be the only laboratory finding during acute and chronic infection. Recognition of acute HCV infection in patients with new-onset liver enzyme elevations is clinically important since HCV treatment during the early phases of infection is more efficacious than treatment during the chronic phase.^{30,31}

Cirrhosis develops in approximately 20% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.^{32,33} Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.^{33,34} HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly in those with advanced immunodeficiency (CD4 T-

lymphocyte [CD4] count <200 cells/mm³).^{35,36} Further, coinfecting patients with cirrhosis progress more rapidly to life-limiting outcomes such as end-stage liver disease and hepatocellular carcinoma (HCC) than do those who are HCV-monoinfected.^{37,38} Because of its high prevalence and accelerated progression, HCV disease is a leading non-AIDS cause of death in HIV-infected individuals.³⁹⁻⁴¹ In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all HIV-infected patients should undergo routine HCV screening. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.⁴² For at risk HCV-seronegative individuals, HCV antibody testing is recommended annually or as indicated by risk exposure.

False-negative anti-HCV antibody results are possible but are uncommon (<1%) in HIV-infected patients with advanced immunosuppression.^{43,44} In addition, negative anti-HCV antibody results can occur during acute infection. Following acute HCV infection, the duration of the window period prior to seroconversion is highly variable, ranging from 2 weeks to 12 weeks. Serum ALT levels are frequently elevated early in the course of acute infection and high ALT levels should prompt testing for HCV RNA if serologic test results are negative or indeterminate in individuals at risk of HCV infection.⁴⁵

Individuals who test positive for HCV antibody should undergo confirmatory testing by using a sensitive quantitative assay to measure plasma HCV RNA level. Importantly, plasma HCV RNA viral load does not correlate with HCV disease severity, and therefore, should not be monitored serially in patients not taking HCV treatment. Plasma HCV RNA levels do provide important prognostic information about the likelihood of response to HCV treatment.

Preventing Exposure

The primary route of HCV transmission is drug injection via a syringe or other injection paraphernalia (i.e., “cookers,” filters, or water) previously used by an infected person. HCV-seronegative injection drug users should be encouraged to stop using injection drugs by entering a substance abuse treatment program or, if they are unwilling or unable to stop, to reduce the risk of transmission by never sharing needles or injection equipment.⁴⁶⁻⁴⁸ HCV also can be transmitted sexually, especially between HIV-infected MSM. HCV-seronegative patients must be counseled regarding the risk of sexual acquisition. The effectiveness of male condoms in reducing HCV transmission is unknown, nonetheless, barrier precautions are strongly recommended to reduce the risk of STDs, including HCV (**BIII**).⁴⁹

Preventing Disease

There is no vaccine or recommended post-exposure prophylaxis to prevent HCV infection. Following acute HCV infection, chronic infection may be prevented within the first 6 to 12 months after infection through antiviral treatment; relatively high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.^{50,51} However, patients also have the potential for spontaneous clearance after acute infection; as such, some experts recommend observation of acutely infected patients—particularly those whose infection (e.g., those with C/C IL28B genotype) is more likely to resolve—for approximately 3 to 6 months before initiating HCV treatment.⁵² In the setting of evolving data, recommendations for management of acute HCV infection in HIV-infected patients are expected to change rapidly. Clinicians should refer to the most recent HCV treatment guidelines (<http://www.hcvguidelines.org>) for the most up-to-date guidance.

HCV-infected individuals should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (as alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day), and avoiding iron

supplementation in the absence of documented iron deficiency.⁵³ HCV-infected patients should be tested for previous or concurrent hepatitis B virus (HBV) infection because co-infection with HBV is associated with increased morbidity. Those without evidence of immunity to HBV should be vaccinated (see [Hepatitis B Virus Infection](#) section). Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in HCV-infected individuals, these patients should be screened for immunity (HAV IgG or antibody total) and those susceptible should be vaccinated (**BIII**).

Coinfected patients with cirrhosis are at risk of life-threatening complications and should be managed in consultation with a gastroenterologist or hepatologist. In particular, individuals with cirrhosis should undergo serial screening for HCC;⁵⁴ some experts recommend performing ultrasonography at 6- to 12-month intervals, although the optimal screening strategy is unknown. Because of its relatively poor specificity and sensitivity, alfa-fetoprotein should not be the sole screening method. HIV infection is not an absolute contraindication to liver transplantation; accordingly, coinfecting patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression. Coinfected patients should be treated with ART in accordance with the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) developed by the Department of Health and Human Services Panel.⁵⁵ Dose adjustment of certain ARV agents may be needed in patients with decompensated cirrhosis.

Treating Disease

In general, the goals of therapy, treatment regimen, and monitoring parameters for HIV/HCV coinfecting patients are similar to those recommended for HCV monoinfected patients. The field of HCV drug development is evolving rapidly. The armamentarium of approved drugs is likely to expand considerably in the next few years. Clinicians should refer to the most recent HCV treatment guidelines (<http://www.hcvguidelines.org>) for the most up-to-date recommendations.

Special Considerations During Pregnancy

Pregnant HIV-infected women should be tested for HCV infection to allow appropriate management for the mothers during pregnancy and after delivery, and also for their infants.⁵⁶ HCV treatment with PegIFN and ribavirin is **contraindicated** during pregnancy (**AII**). IFNs are abortifacient at high doses in monkeys and **should not be used** in pregnant women because of their direct antigrowth and antiproliferative effects.⁵⁷ Ribavirin is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia. Ribavirin **should not be used** during pregnancy (**AII**). Women of childbearing potential and men receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy (**AIII**). Inadvertent pregnancy during paternal exposure was not associated with adverse events in two newborns.⁵⁸ Pregnancies that occur in women taking ribavirin or those in women whose male partner is taking the drug should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or <http://www.ribavirinpregnancyregistry.com>). Telaprevir, boceprevir, and sofosbuvir are Pregnancy Category B and simeprevir is Pregnancy Category C; however, these agents are often used in combination with PegIFN/ribavirin, which are **not recommended** in pregnancy. The FDA category assignment for these novel drugs, though, is based on safety in animal studies as there are no human data available.

Evaluation of HCV-infected pregnant women, including liver biopsy, can be delayed until >3 months after delivery to allow potential pregnancy-related changes in disease activity to resolve. HAV and HBV vaccines can be administered during pregnancy and women who have not previously been vaccinated should receive them. Several studies have reported that perinatal transmission of HCV occurs more frequently in women with HIV/HCV-coinfection than in those with HCV mono-infection. However, data are limited regarding the role of

medical or surgical interventions to reduce the risk of perinatal HCV transmission. Nearly all studies, including those in HIV-uninfected and HIV-infected women, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.^{26,59-61} Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.⁶²⁻⁶⁵ Thus, while elective cesarean delivery in HIV/HCV-coinfected women can be considered based on HIV-related indications, data are insufficient to support its routine use for prevention of HCV transmission.

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